Review Article

High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective

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The role of low grade systemic inflammation as evidenced by elevated high sensitivity C-reactive protein (hsCRP) levels in the pathogenesis of atherosclerotic vascular disease has been intensely investigated through observational studies and clinical trials in the past two decades. On the basis of evidence that has accrued, hsCRP measurement has been integrated into the Reynolds risk scoring system to predict cardiovascular risk. The JUPITER trial proved the benefit of statins in cardiovascular risk reduction in patients with low grades of systemic inflammation and 'normal' cholesterol levels. However, substantial evidence has been generated from western studies. We, therefore, conducted a scoping review for studies done in India with a view to identify gaps in evidence and make further recommendations. Most Indian studies had small sample sizes and short term follow ups. There were no large population based prospective studies where patients were followed up for long periods of time for major cardiovascular end points. An analysis of the hsCRP level from the control arms of case-control studies derived a mean hsCRP value of 1.88 mg/l, which is higher than the western population where values < 1 mg/l are classified as low cardiovascular risk. Further large prospective cohort studies with longer term follow ups are essential before we can make further recommendations to integrate hsCRP into risk prediction models for cardiovascular disease prevention.

Key words Atherosclerosis - cardiovascular disease - hsCRP - India - inflammation - myocardial infarction

Introduction

The role of inflammation in the pathogenesis of atherosclerosis has been firmly established in the past two decades. Numerous studies, both observational (nested case control and prospective cohort) and randomized controlled trials (RCTs) have shown an association of pro-inflammatory biomarkers with incident hypertension, metabolic syndrome, coronary artery disease (CAD), acute coronary syndrome (ACS), peripheral artery disease, stroke and recurrent coronary and cerebrovascular events[1-4]. Approximately 25 large observational studies published since the 1990s have established high sensitivity C-reactive protein (hsCRP), a biomarker of inflammation, as an independent predictor for CAD. A meta-analysis of these observational studies showed that people in the top quartile for hsCRP levels had an odds ratio (OR) of 1.5 compared with those in the lowest quartile for major

cardiovascular events, after adjusting for established risk factors[5]. Apart from observational studies, several RCTs evaluating statins such as Pravastatin or Atorvastatin Evaluation and Infection Therapy– Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI-22)[6], Cholesterol and Recurrent Events (CARE)[7], The Pravastatin Inflammation/CRP Evaluation (PRINCE)[8], Aggrastat- to- Zocor (A to Z)[9] and Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)[10] indicate that cardiovascular benefits are more apparent when systemic inflammation (as evidenced by hsCRP reduction) is reduced in addition to intensive low-density lipoprotein cholesterol (LDL-C) lowering. The A to Z trial[9] demonstrated that the best clinical outcomes occurred when the hsCRP levels were lowered below 2 mg/l in addition to LDL-C lowering to < 70 mg/dl. An imbalance between pro- and anti-inflammatory factors contributes to the atherosclerotic process. Inflammatory processes have an effect on the integrity of the fibrous cap in atherosclerotic plaque. Pro-inflammatory processes involving innate and adaptive immune mechanisms weaken the fibrous cap, causing a predisposition towards its rupture[2]. Interferon-γ (IFN-γ) elaborated by activated T cells suppresses collagen production by smooth muscles cells of the arterial wall. This is coupled with enhanced collagen degradation in the fibrous cap mediated by the matrix metalloproteinase enzymes (MMP-1, MMP-8, MMP-13) synthesized by activated macrophages. These processes enhance the friability of the fibrous cap[11].

Currently it is being tested whether interventions to suppress the inflammatory process at "key points" in the inflammatory cascade can modify the atherosclerotic process and reduce clinical events.

What are CRP and hsCRP?

C-reactive protein (CRP) is a member of the pentraxin family of proteins. It is an acute phase reactant synthesized mainly by the liver. Serum CRP levels are elevated in response to acute infections, inflammatory conditions and trauma. In these clinical situations, the serum CRP levels rise rapidly generally beyond 10 mg/l with a concomitant elevation of erythrocyte sedimentation rates (ESR)[12]. CRP has a relatively long half-life of 18 to 20 h, owing to its stable pentraxin structure. In addition, CRP levels are stable as these do not exhibit diurnal variations or variations in relation to food intake. In the past decade, high-sensitivity assays

with rapid turnaround times for measurement have become available. High-sensitivity assay techniques such as immunonephelometry, immunoturbidimetry, high-sensitivity enzyme-linked immunosorbent assay (ELISA) and resonant acoustic profiling (RAP) can detect CRP with a sensitivity range of 0.01 to 10 mg/l[13]. These high-sensitivity assays help quantify low grades of systemic inflammation, in the absence of overt systemic inflammatory or immunologic disorders. The hsCRP assays have been standardized across several commercial platforms and can be accurately measured from fresh or frozen plasma[14]. The hsCRP is the most widely evaluated biomarker in the quest for an ideal biomarker for global cardiovascular disease (CVD) risk prediction. It has been incorporated into the Reynolds Risk Scoring system for global CVD risk prediction in women and along with a parental history of premature myocardial infarction can reclassify 50 per cent of all women in the ATP III intermediate risk category (annual CVD risk of 5 to 10%) and 10 to 20 per cent into higher or lower 10-year risk categories, with improved accuracy[15]. On the basis of data obtained from population based studies, the AHA/CDC (American Heart Association/Centres for Disease Control) Working Group on markers of inflammation in CVD has classified serum hsCRP levels <1, 1–3 and >3 mg/l as low-, intermediate-, and high-risk groups for global CVD, respectively[13]. The Working Group recommends conducting two hsCRP assays two weeks apart in a fasting or a non-fasting state in a metabolically stable patient with no obvious signs of infection or inflammation that could confound results.

Although hsCRP has largely been the central focus, other inflammatory markers such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-7 and the matrix metalloproteinases have also been associated with the atherosclerotic process[2]. Several factors, however, make hsCRP an attractive biomarker for cardiovascular risk prediction.

Is hsCRP just a marker of inflammation or does it play a causative role?

A debated controversy in this area has been whether hsCRP contributes to the atherosclerotic process or is merely a marker of inflammation. The hsCRP has been noted to have opsonizing properties, increasing the recruitment of monocytes into atheromatous plaque and also inducing endothelial dysfunction by suppressing basal and induced nitric oxide release. The hsCRP *per se* has also been found to increase the expression of

vascular endothelial plasminogen activator inhibitor-1 (PAI-1) and other adhesion molecules and alter LDL uptake by macrophages[11]. However, interventions that directly inhibit hsCRP would have to be evaluated before conclusively establishing hsCRP as a direct contributor to the atherosclerotic process. Mendelian randomization studies have hinted at a causal relationship between hsCRP genotypes and atherosclerotic CVD, though stronger evidence of causality is required[16].

What were the lessons from JUPITER?

JUPITER – a primary prevention trial[10] sought to evaluate the utility of a statin in reducing major adverse cardiovascular events in patients with normal to low cholesterol levels (LDL-C <130 mg/dl) but with high hsCRP levels (>2 mg/l). A total of 17,802 apparently healthy men and women were randomized to receive either rosuvastatin 20 mg or placebo. The trial was stopped prematurely within a median follow up duration of 1.9 yr, as rosuvastatin produced a significant reduction in the pre-specified primary composite end point of myocardial infarction, stroke, cardiovascular death, arterial revascularization and unstable angina. Rosuvastatin was shown to reduce LDL-C levels by 50 per cent and hsCRP levels by 37 per cent. The overarching question that this trial posed was whether the beneficial effects on cardiovascular end points were due to lipid lowering alone, suppression of inflammation alone (as demonstrated by hsCRP reduction), or a combination of both mechanisms. JUPITER did not address the question of whether selective suppression of the inflammatory process could also achieve beneficial effects. The ongoing Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial[17] attempts to provide better clarity on the questions raised by the JUPITER trial.

What can CANTOS tell us?

The CANTOS (ClinicalTrials.gov Identifier NCT01327846) trial addresses this controversy; it evaluates if selective inhibition of IL-1β with canakinumab can reduce cardiovascular death, non-fatal myocardial infarction and stroke in stable post-myocardial infarction patients at high risk for recurrent events as evidenced by serum hsCRP >2 mg/l. Phase 2 trials with canakimumab have shown that upstream inhibition of IL-1β resulted in dose dependent 50 per cent reductions in downstream biomarkers, CRP and IL-6 levels, without lowering lipid levels or blood pressures[18]. The results of the trial are expected in 2018.

The large numbers of Western studies that have evaluated the link between hsCRP and cardiovascular disease, prompted a scoping review of the studies conducted in India linking the inflammatory hypothesis in general and hsCRP in particular, with metabolic syndrome and CVD. The objectives of this article are to review the studies linking the inflammatory hypothesis with diabetes mellitus, metabolic syndrome and atherosclerosis in the South Asian/Indian population, to identify gaps in evidence and to make recommendations for further work in this important area in the Indian context.

Literature search methods

The search was done using PubMed and Google Scholar. We used the following search strings: hsCRP in India AND type 2 diabetes mellitus AND cardiovascular disease, hsCRP in Indian patients, hsCRP in Indian population, hsCRP in India AND cardiovascular disease. No limits were set in order to retrieve a maximum number of articles.

A total of 71 articles were retrieved from PubMed and 1400 articles were retrieved from Google Scholar. The abstracts were reviewed and a total of 27 articles (14 from PubMed and 13 from Google Scholar) that had hsCRP measurements in patients with cardiovascular disease and/or type 2 diabetes mellitus, were selected. Studies conducted in Indian patients that explored the relationship between hsCRP as a marker of inflammation and outcomes such as type 2 diabetes mellitus, impaired glucose tolerance and primary or secondary prevention of coronary artery disease were included. Studies that were not conducted in India, evaluated inflammatory markers other than hsCRP or evaluated the relationship of hsCRP with outcomes other than the ones specified were excluded.

The studies included

Of the 24 studies (Table), 12 (50%) were case-control studies, six (25%) were cohort studies and six (25%) were cross-sectional studies. Of the six cohort studies, four (66.6%) were comparative studies performed in a nested cohort of patients, one (16.6%) was a retrospective and one (16.6%) was a prospective cohort study. Eight (33.3%) studies evaluated the utility of hsCRP as a predictor for diabetes mellitus, nine (37.5%) evaluated hsCRP levels in patients with metabolic syndrome including diabetes, six (25%) studies correlated hsCRP levels with abdominal adiposity and body mass index. Ten (41.6%) studies

S. no.	Author	Design	n	Outcome	Control hsCRP value (mg/l)
	Table. Summary of Indian studies evaluating hsCRP as a risk predictor				
1.	Asegaonkar et al[19] (2011)	Case-control	120	hsCRP levels correlate with T2DM	0.9
2.	Bhagwat et al[20] (2012)	Cross-sectional	101	hsCRP increased in diabetes, diabetes with hypertension & MI	1.22
3.	Chowta et al[21] (2012)	Cross-sectional	40	hsCRP levels higher in patients with CVD than no CVD	3.83
4.	Dambal et al[22] (2013)	Cross-sectional	30	hsCRP higher in patients with T2DM with acute MI than acute MI without type 2 diabetes	7.19
5.	Ghodke et al[23] (2012)	Case-control	200	hsCRP may be an indicator of CAD	Unreported
6.	Garg et al[24] (2012)	Case-control	74	hsCRP and other inflammatory markers associated with BMI, per cent body fat, HOMA-IR and other components of metabolic syndrome	2.09
7.	Gokulakrishnan et al[25] (2008)	Comparisons in a nested cohort	450	hsCRP associated with glucose intolerance and carotid IMT	N/A
8.	Gokulakrishnan et al[26] (2009)	Nested cohort	865	hsCRP and leucocyte count correlates with metabolic syndrome and other CV risk factors	1.35
9.	Goswami et al[27] (2011)	Case-control	200	hsCRP is an independent predictor of CAD	0.3
10.	Guruprasad et al[28] (2012)	Case-control	442	hsCRP associated with increasing severity of CAD	0.35
11.	Jaiswal et al[29] (2012)	Case-control	1726	hsCRP independently associated with IFG & IGT	1.64
12.	Jeemon et al[30] (2011)	Comparisons in a nested cohort	600	BMI and abdominal adiposity can be surrogates for elevated hsCRP levels	N/A
13.	Mahadik et al[31] (2008)	Retrospective cohort	267	hsCRP correlates with central obesity and is a predictor	3.06
14.	Mahajan et al[32] (2009)	Cross-sectional	2520	hsCRP independent predictor of type 2 diabetes mellitus	1.22
15.	Mahajan et al[33] (2012)	Cross-sectional	9517	hsCRP independently predicts the risk of metabolic syndrome, apart from obesity and insulin resistance	1.49
16.	Mahajan et al[34] (2009)	Case-control study	140	hsCRP in addition to MMP-9 & TIMP-1 is associated with increased CAD severity	1.68
17.	Misra et al[35] (2012)	Case-control	71	hsCRP is an independent predictor of diabetes and metabolic syndrome	0.44
18.	Mohan et al[36] (2005)	Comparisons in a nested cohort	150	hsCRP is an independent predictor of CAD in diabetic patients and correlates with increasing body fat	0.99
19.	Nyandak et al[37] (2007)	Cross-sectional	73	hsCRP associated with increasing severity of angiographic lesions	2.28
20.	Rajeshwar et al[38] (2012)	Case-control	1156	hsCRP and NO levels predict the occurrence of ischaemic stroke	N/A

Contd...

S. No.	Author	Design	n	Outcome	Control hsCRP value (mg/l)
21.	Rao *et al*[39] (2010)	Prospective cohort	1021	hsCRP is an independent predictor of a repeat coronary event	2.81
22.	Roopkala *et al*[40] (2012)	Case-control	75	hsCRP associated with increased risk of diabetic nephropathy	2.75
23.	Shalia *et al*[41] (2012)	Case-control	200	-717 A/G genotype does not influence hsCRP level; hsCRP level correlates with BMI and triglycerides	Mean N/A; 76% participants had hsCRP range of 1 – 10 mg/l
24.	Thakur *et al*[42] (2011)	Case-control	200	hsCRP concentration elevated in CHD subjects	0.93

ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment-estimated insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MMP-9, matrix metalloproteinase enzyme; NO, nitric oxide; T2DM, type 2 diabetes mellitus; TNF-α, tumour necrosis factor-α. Superscript numerals denote reference numbers

reported the utility of hsCRP as a predictor of CAD and two (8.3%) studies as cerebrovascular disease. Only five (20.8%) of the 24 studies have large sample sizes (n > 1000) of which only one was a prospective study and three were case-control studies. None of the studies evaluated parameters such as sensitivity, specificity, positive and negative predictive values of hsCRP in cardiovascular risk prediction.

Of the 24 studies, control group patients in at least 13 (54.2%) studies had hsCRP levels in the intermediate to high risk group level (>1 mg/l), indicating that the basal concentration of hsCRP is high in Indians. An analysis of the control arm of the various studies derives a mean hsCRP value of 1.88 mg/l. In studies with subjects having established CVD, the hsCRP values varied from 2.46 to 9.3 mg/l. Similar results have been found among Asian Indians living in the United Kingdom, where Indians were found to have 17 per cent higher CRP values compared with Europeans[43], among Indians living in the United States as compared with Caucasians[44], and among Indians in Singapore as compared with the Chinese and the Malays[45]. The included studies employed a wide range of analytical techniques for hsCRP estimation; eight (33%) studies employed ELISA, six (25%) employed nephelometry, seven (29%) used turbidimetry, two (8.3%) used chemiluminescence and in one study latex agglutination test was used for quantification. This could have contributed to the varying values seen across these studies.

Implications of the Indian studies so far

The hsCRP was found to be an independent predictor of diverse end points ranging from obesity, type 2 diabetes mellitus, metabolic syndrome, increased carotid intima-media thickness, stable CAD, first acute coronary event, and recurrent CVD events. The larger studies have mainly evaluated the association of hsCRP and risk factors for CVD, diabetes mellitus and glucose intolerance. Mahajan *et al*[32], in a study of 2,520 subjects, reported hsCRP to be an independent predictor of type 2 diabetes mellitus (OR, 1.66; 95% CI, 1.21 – 2.28, *P*=0.002). In another study, a cross-sectional survey of 9,517 subjects[32], the authors again found an association between hsCRP levels and metabolic syndrome, obesity and insulin resistance (OR, 1.65; 95% CI, 1.41 – 1.92). Jaiswal *et al*[29] in a case-control study of 1,726 subjects, reported hsCRP to be independently associated with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (OR, 2.60; 95% CI, 1.56 – 5.34). Studies with clinical CVD events included a case-control study by Rajeshwar *et al*[38] (1,156 subjects; hsCRP levels predict ischaemic stroke), Goswami *et al*[27] (200 subjects; hsCRP is an independent predictor of CAD) and Guruprasad *et al*[28] (442 subjects; hsCRP levels are associated with an increasing severity of CAD). A prospective cohort study by Rao *et al*[39] with 1,021 subjects, of whom 772 had established CAD and the rest were controls, found that hsCRP was an independent predictor of repeat coronary events.

The published studies from India have thus reported an association between hsCRP and metabolic syndrome, IGT, diabetes mellitus, CAD, and stroke. These studies used different designs and methods of estimating hsCRP and at times used arbitrary cut-off levels. A majority of these studies had small sample sizes and were case-control, cross-sectional or retrospective cohort studies. It is, therefore, not possible to define normal values and cut-off levels as identifiers of risk specifically for the Indian population from these studies. This is particularly important as current evidence points to elevated basal levels of hsCRP even in the normal control group patients. If one has to define a specific value and range as normal for Indian subjects and cut-off values for estimation of risk for CVD, data from large high-quality studies are needed to permit the construction of a receiver operating characteristic (ROC) curve. To achieve this, it is important to initiate large prospective cohort studies with standardization of diagnostic tests across sites and adequate follow up of participants for cardiovascular outcomes to derive risk cut-off values in the Indian population. Such studies are also needed to estimate the role of hsCRP versus other risk factors such as lipids to justify the recommendation and/or of routine measurement of hsCRP in estimating the risk for CVD in Indian patients.

Conclusion

Multiple small Indian studies employing varying designs have found an association between hsCRP and coronary artery disease, diabetes mellitus and the metabolic syndrome. The normal or basal values of hsCRP are likely higher in the Indian population. Larger prospective cohort studies employing standardized hsCRP measurement assays with adequate follow up duration are required to derive risk cut-off values for CVD in the Indian population.

Conflicts of Interest

Dr Prem Pais is the National Leader for the CANTOS study in India. The other authors declare no conflicts of interest.

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